Centro Nazionale Trapianti
Italian National Transplant Centre
WHO Collaborating Centre on Vigilance and Surveillance for Human Cells, Tissues and Organs

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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Keeping MPHO safe - monitoring adverse outcomes and scanning for new threats.

A Joint ECDC and WHO NOTIFY project meeting

October 1st and 2nd 2020 – ZOOM platform

This publication reports on the deliberations and outcomes of the Keeping MPHO safe - monitoring adverse outcomes and scanning for new threats. A Joint ECDC and WHO Notify project Virtual meeting. The meeting has been organized by the Italian National Transplant Centre, WHO Collaborating Centre for vigilance and surveillance of Human cells, tissues and organs, in the framework of WHO's activities in the area of Medical Products of Human Origin (MPHO).

This meeting was made possible thanks to the kind invitation of the European Centre for Disease Prevention and Control (ECDC) who provides longstanding support to the Notify project. The joint effort of these organizations to organize a meeting devoted to monitoring adverse outcomes and scanning for new threats, provided potential for effective networking and collaboration between public health specialists working in the field of MPHO safety at a global level.

Given the exceptional combination of vigilance expertise that exists in the NOTIFY experts group, the meeting was the perfect opportunity to share experiences of the impact of the COVID-19 pandemic on MPHO and to agree and document the key lessons learned in a dedicated session.

The meeting brought together the NOTIFY project editorial groups and the steering committee, as well as new invited experts from international vigilance and surveillance authorities, with the aim to focus on horizon scanning and preparedness for future threats to MPHO safety and on reinforcing the global MPHO vigilance network.

WHO is gratefull to CNT and the NOTIY team for their support in organizing the consultation, and we would like to specifically thank Massimo Cardillo (Chairman of the meeting) and Claudia Carella with Aurora Navarro (Rapporteurs) for their efficiency.

Furthermore, WHO would like to acknowledge the invaluable contributions of Mike Strong, Deirdre Fehily, Evangelia Petrisli, Matthew Kuenhert and Dragoslav Domanovic who acted as a scientific committee.

Finally yet importantly, we want to thank all the participants in the consultation, for their active participation and their will to achieve consensus. This report was submitted to everyone and we are grateful for their comments and input. The recommendations, statements and positions set out in the following report are based on the ideas and suggestions that were presented by the individual experts or raised during the event discussions. They do not necessarily reflect the views or stated policy of the WHO or other participating organizations, agencies and institutions.

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FINAL REPORT

The eighth general meeting of the NOTIFY project, scheduled to be hosted by the European Centre for Disease Prevention and Control (ECDC) in Stockholm, took place by video conference due to the COVID-19 pandemic. This report highlights the major topics discussed, gives an overview of the work carried out since the last general meeting by the Editorial Groups and describes some agreed actions to take forward. Pivotal to this meeting was the support provided by WHO officers and consultants and by ECDC who organized the programme in cooperation with CNT.
The rapporteurs for the meeting were Claudia Carella and Aurora Navarro.
The first part of the meeting was moderated by Dr Dragoslav Domanovic.

Welcome address from ECDC
Dr Piotr Kramarz, Deputy Chief Scientist and Deputy Head of the disease programmes unit at ECDC, welcomed the participants. ECDC had been enthusiastic to host this meeting in Stockholm, given their central role in European Union to monitor communicable disease risks and recommend actions to prevent disease transmission during outbreaks. ECDC relies on the expertise of external experts and was looking forward to the outcome of the meeting.

Welcome address and objectives of the meeting
Dr Massimo Cardillo, Director General of CNT welcomed the participants. He expressed his appreciation to ECDC for accepting an active role in the organization of this meeting. CNT appreciates the value and continuous support given by ECDC to the NOTIFY Project. CNT is also very grateful to representatives of the regional WHO offices for being the champions of NOTIFY around the world.
Dr Cardillo noted that the NOTIFY project has a long history and has had success thanks to the cooperation of all the editorial group members, the NOTIFY operational team and all the esteemed experts that continue to provide input to the project strategy.
The pandemic brought new challenges to the world of Medical Products of Human Origin (MPHO). The **aim** of this meeting was to focus on **horizon scanning** and **preparedness planning** for future threats to the donation and clinical application of MPHO and on **reinforcing the global MPHO vigilance network.** During these two days, participants would have the opportunity to **share experiences** on the impact of the COVID-19 pandemic on MPHO safety and availability and to **document the key lessons learned.**

Welcome address from WHO
Yuyun Maryuningsih, Team Lead for Blood and other Products of Human Origin at WHO, welcomed the group and congratulated the CNT, as a WHO Collaborating Centre, and ECDC for hosting the meeting in cooperation with CNT. Over the years, NOTIFY has expanded the work to include blood products which was highly appreciated by WHO. The Covid-19 crisis had provided a trigger to build a global MPHO preparedness network and all the parties involved in NOTIFY were invited to contribute their efforts to achieve this goal.

Closing the circle of vigilance reporting and preparedness planning
Deirdre Fehily, Policy Officer, seconded from CNT to the European Commission, DG Santé Substances of Human Origin team, introduced the concept of the meeting. Since the first meeting in 2011, the NOTIFY Library has focused its work on the sharing of lessons from vigilance to help prevent adverse outcomes in transfusion, transplantation, and assisted reproduction. The aim has been to take what has been reliably reported and to make the information easily available to all those working in these fields. The editorial groups of experts build the records and link them to their references. The general

principles are encapsulated in the NOTIFY 'Booklet' on Vigilance and Surveillance of Medical Products of Human Origin.
She stressed that the approach to date represents just one part of the vigilance and surveillance (V&S) circle because adverse occurrences can also be prevented. Many organisations scan the horizon for new risks. Experts need to evaluate whether these have implications for MPHO and whether preventative measures should be taken. The ongoing pandemic had highlighted the need to address new emerging disease threats to MPHO rapidly, allowing a wider proactive approach. In this context, she proposed that the NOTIFY Library could support the communication of risk and possible mitigation measures to close the V&S circle.

The meeting organizers had invited WHO, US CDC, ECDC and African CDC to present the approach within these organisations to scanning for communicable disease outbreaks. Unfortunately, it was not possible for a representative from the African CDC to participate in the meeting.

Scanning for communicable disease outbreaks WHO perspective

Junping Yu, WHO, presented the response of the organisation to address the impact of emerging infections to blood safety and supply. The International Health Regulations (IHR) 2005, adopted on May 2005 by the 58th World Health Assembly, provide algal framework for early detection, reporting and response to outbreaks of infectious disease. In addition to a short list of diseases subject to mandatory notification to WHO, countries are also required to assess the international public-health threat posed by any unusual health event, including those of unknown causes or sources. WHO can use a range of sources of health intelligence to raise an alarm and begin a process of verification with countries that have not voluntarily reported significant health events.
Epidemic intelligence (EI) encompasses all activities related to early identification of potential health hazards, their verification, assessment, and investigation to recommend public health control measures. EI integrates both an indicator-based component related to data collected through routine surveillance systems and an event-based component which refers to unstructured data gathered from sources of intelligence of any nature.
In 2017 WHO launched an EIOS initiative: Epidemic Intelligence from Open Sources (available at the link https://www.who.int/eios). The EIOS initiative is led by WHO under the Health Emergencies Programme (WHE) with a governance structure involving multiple stakeholders forming the Coordination Group (CG). It brings together new and existing initiatives, networks, and systems to create a unified all-hazards, One Health approach to early detection, verification, assessment, and communication of public health threats, using publicly available information.
It is aimed at consolidating a wide array of endeavours and platforms to build a strong public health intelligence (PHI) community supported by robust, harmonised and standardised PHI systems and frameworks across organisations and jurisdictions. The EIOS initiative benefits from the experience gained in the Early Alerting and Reporting (EAR) project of the Global Health Security Initiative (GHSI), the Hazard Detection and Risk Assessment System (HDRAS) and MEDISYS/Europe Media Monitor and finally connects to other systems and actors, including ProMED, HealthMap and the Global Public Health Intelligence Network (GPHIN).
Since 2003, WHO has provided guidance, information and tool to support the national blood services during the major disease outbreak of global concern and developed the "Risk-Based Decision Support Tool for Blood Safety". Specific guidelines related to blood safety and availability (latest version dated 2019 available at the link: https://www.who.int/bloodsafety/publications/protecting-blood-supply/en/ (last access: 20/02/2021)
One of priority of WHO BTT work is to strengthen the surveillance, response, and preparedness of the national blood system to address emerging infections. This encompasses the need to establish a

formalized global mechanism, to ensure a systematic approach and to maximise benefits and thus to help countries to better prepare their blood systems for the next disease outbreak.

Scanning for communicable disease outbreaks US CDC perspective

Jefferson Jones from the Office of Blood, Organ and other Tissue Safety of the US Centers for Disease Control and Prevention presented an overview of V&S systems in the US. The major goal of the public health surveillance system is to measure the burden of a disease, monitor trends in the burden of a disease, guide immediate action for cases of public health importance to include active and passive reporting and data components to facilitate incidence and prevalence estimation.

The regulation of MPHO in the US is threefold: the Food and Drug Administration has the regulatory authority over blood and blood products, tissues, and cell therapies (approval of screening tests as well), the Health Resources and Service Administration has oversight over solid organ transplantation; hospital oversight is carried out by accrediting organizations and state governments.

Challenges in hemovigilance and other MPHO vigilance have been reported, resulting in opportunities to improve monitoring of MPHO safety:

For blood → to improve the participation in the Hemovigilance Module for reporting adverse occurrence (passive reporting) which is not mandatory.

For organs → to establish standardised criteria for what needs to be reported and to perform ongoing analysis and report data to detect trends

For tissues → to adopt common nomenclature and coding for tissue specific donors; to establish tissue traceability requirements, including when organs and tissues come from the same donor and to establish a surveillance system for adverse events.

Scanning for communicable disease outbreaks ECDC perspectives

Thomas Mollet, Head of the Epidemic Intelligence unit at ECDC, in responsible for detecting, monitoring, and assessing new threats; collecting, validating and analysing the information gathered; performing risk assessments and issuing recommendations for public health measures. Since 2005, ECDC has implemented a new system that complements the classical surveillance at the EU level, to produce rapid risk assessments within a shorter timeframe.

The Threat Detection office performs monitoring 24/7. This epidemic intelligence team detects relevant signals and reports them during a daily round table meeting. If the detected threat might have an impact on EU populations, a team of 5-10 experts produces a rapid risk assessment that is published on the ECDC website.

At the EU level, the European Surveillance System (TESSy) collects information from the Member States and shares it with international stakeholders. A parallel digital platform, the EWRS (Early Warning and Response System) is a key tool for EU Member States to detect threats to public health. Each Member State can share information and preparedness plans through EWRS. The ECDC EPIS (epidemic intelligence information system) is open to 70 countries and will be complemented with the development of EPIPULSE.

It was noted that social media monitoring has been an important source of information on new outbreaks; 30% of signals were detected from Twitter before they were posted on official institutional websites. EpitweeTr is a dedicated tool used to analyse worldwide tweets. The tool, which is available at the link https://www.ecdc.europa.eu/en/publications-data/epitweetr-tool, is free and it can be customized by language and keywords. Considerable effort is also dedicated to detecting fake news that is circulating on social media.

In terms of output, the ECDC round table and the Communicable Diseases Threat reports (CDTR) are publicly available on the EDCD website together with further documents such as rapid risk assessments, mass gathering reports and annual threat reports.

Q&A session

In the Q&A session, the following was highlighted:

- *In the United States, epidemic intelligence signals are communicated directly from the central administration of CDC which works with its regulatory partner, FDA, and the main scientific and professional organizations/associations.*
- *ECDC would be available to share the EPI tool with US CDC. A weekly exchange is already established with US institutions.*
- *The EIOS initiative led by WHO performs the same intelligence surveillance globally.*

To conclude the session: The scanning for communicable disease outbreaks, frequently referred to as Emerging Infectious Diseases, (EID), can be described as a systematic collection and collation of information from a variety of sources, which is then validated and analysed. The aim of these systems is to ensure a timely response based on adequate risk assessments with recommendations on appropriate public health measures. Detecting signals of infectious disease outbreaks is core to international, national, and regional public health bodies such as CDC, ECDC, WHO and other public health institutions. As part of this process, they also analyse whether the detected infectious diseases may impact the safety of MPHO. Once identified, MPHO threats are communicated to relevant experts in the responsible bodies, who assess the risk of transmission through MPHO and recommend preventive measures.

The second part of the meeting was moderated by Matthew Kuehnert and focused on MPHO and the COVID-19 pandemic. A panel of Global experts were invited to share their experience and the lessons learned focusing on safety, sustainability of supply and the use of MPHO in treating infected patients. They were asked to highlight any lessons learned regarding how countries could improve their responses in similar situations in the future.

- **Jay Epstein** (*Senior Advisor for International Blood Regulatory Affairs, CBER, FDA - Informal consultant to WHO*)

  Dr Epstein has long-standing experience in blood safety information gathering, analysis, policy making, and rapid response. He noted that, in terms of improving preparedness, three different domains should be considered, namely prediction, ongoing epidemiological intelligence and capacity for response. The first concerns what can be predicted based on the available knowledge. There have been efforts in this direction. For example, FDA has convened, in the past, several workshops related to specific viruses to highlight possible threats and to translate them into preparedness plans. The second important domain is epidemiological intelligence. One of the challenges to the effective assessment of risks is the exchange of samples from donors or recipients internationally. This aspect has posed an enormous barrier historically and, in recent years, it emerged particularly with efforts to address MERS and ZIKA.

  In the domain of improving response capacity, it is important to think about pathogen transmission by product type, but also to consider the capacity of the outbreak to cause massive system disruption. The lesson from COVID 19, particularly for the blood supply, is the relevance of system disruption. Experts tend to focus on intrinsic threats. However, threats to system integrity that were evident in the SARS-CoV-2 pandemic serve as a reminder to consider the system as a whole. Similar to epidemics, natural disasters and bioterrorism can pose threats both to product safety and integrity of the MPHO supply system.

  Various steps can be taken to improve preparedness for epidemics. Specifically, for blood and blood components, there should be a global high-level programme to improve pathogen reduction technologies. Such technologies for red cell transfusion have not improved in years and addressing this could be part of increased preparedness against intrinsic threats of disease transmission.

Another issue is inadequate interaction between the scientific and political actors especially when it comes to the responsibility to communicate information during a pandemic. What is needed are coherent messages that are updated according to the emerging science. The communication response should be managed under a predetermined strategy in which a specified spokesperson within the responsible institution is in continuous contact with the appropriate scientific experts.
Actions to be carried out to avoid system disruption include the proper management of stocks, dynamic inventories and material supply chains. Additionally, rapid access to emergency funds is critical. In this regard, there should be a designated responsibility to keep the system running. In this regard, a better decision-making framework is needed to define where to allocate resources to achieve optimal results.

- **Marisa Herson** – (*General Secretary of the World Union of Tissue Banking Association*).
Marisa Herson shared the experience acquired in tissue and eye banking during the pandemic. The presentation had been prepared with the contribution of several World Union of Tissue Banking Associations (WUTBA) member representatives, eye and tissue bankers and with the contribution of sector data from the Australian Organ and Tissue Authority. She described that the tissue banking community has gone through three different stages since the COVID-19 outbreak started. At the onset, experts were overwhelmed wand the fear of disease transmission through collected tissues halted retrieval and processing. Furthermore, access to PPE became restricted and saved for clinical use and staff from the tissue banks were often redeployed to clinical work. Due to similar fears, there was a decrease in organ donation and transplantation, with reduced consent rates for tissue donation. That had a significant impact on numbers of donations which dropped substantially compared to previous years. The ensuing requirement for staff to work from home impacted on many aspects of tissue banking activities including administration, donor screening and tissue processing. The suspension of elective surgery impacted the number of donations from living donors as well. An additional concern, raised at the beginning of the pandemic, was the difficulty in distributing the available tissues not only within countries but across borders. The supply of some tissues has also been reduced due to unused tissue discard (e.g. corneas). Although the shortage of corneas, bone tissue and cardiovascular tissue were mitigated by the reduced number of elective surgeries where those transplants are used, this was not true for skin. The demand for skin was notably high due to burns happening especially in Australia during the pandemic.
With the second phase, elective surgeries started again, the demand for tissues increased, with a small return of living and deceased donations. However, given the status of the pandemic, eye and tissue banks adopted mitigating measures such as the universal protection of retrieval and processing staff and the completion of medico-social questionnaires addressing specifics to COVID19 to exclude donors posing potential risks. As far as testing is concerned, a large variation of policy and protocols was observed, as well as variable advice form regulatory bodies, both related to living or deceased organ and tissue or tissue-only donors. Some donor testing was performed for psychological reasons, for example, to certify to the potential recipient that the donor was tested COVID-19.
The main take away lessons learned after the first wave of the pandemic can be summarized as follows:
    1. No severe impact on general demand: supply ratio mostly due to reduced elective surgical activity, although there was a negative impact in the availability of specific tissues such as skin for urgent procedures.
    2. No staff SARS-CoV-2 infection through tissue retrieval/processing activities was documented.
    3. No SARS-CoV-2 transmission to recipients was documented.
    4. There was an economic impact on tissue bank sustainability, as some banks were not able to distribute during the pandemic and could not recover their costs.

5. There was profound change in the distribution of tissues across borders, with the establishment of new export/import routes
6. Self-sufficiency in tissue donation and banking within a country or a region is pivotal. Stockpiling or building a global emerging resource system should be considered for the future.

Finally, Dr Herson noted that it took too long to understand the threat, to share information, to organize and respond. In conclusion, she proposed that a shared global platform with other MPHO for harmonized and consistent emergency responses is needed.

- **Matthew Kuehnert** (*US HHS Advisory Committee on Blood and Tissue Safety and Availability*)

Dr Kuehnert presented the lessons learned in US tissue banking from the COVID-19 pandemic. The risk of tissue use is complicated by the fact that the risk of disease transmission is not well quantified, due to the lack of a national surveillance system (biovigilance) for adverse reactions or disease transmission through tissue allografts. He underlined also however that risk is mitigated through processing of tissues in a manner similar to pathogen inactivation for blood. Unfortunately, at this stage, techniques for pathogen reduction of tissues processing are proprietary and not standardized.
Organ donor screening started almost immediately upon recognition of COVID-19 pandemic, due to the concerns raised by the transplant community. The American Society for Transplantation issued recommendations for SARS-CoV-2 screening, suggesting the screening of organ donors with laboratory testing (when feasible). Publications related to viremia in blood donors were taken into consideration as possible risk of transmission through tissue transplantation, and the COVID-19 panel of the AATB physicians council assembled the medical directors of tissue banks to discuss relevant issues and travel deferral was implemented immediately, first from China, then Asia and Europe. Other deferrals were based on clinical symptoms, and included cases of pneumonia without definitive diagnosis; diagnosis of Covid-19, persons under investigation (PUI) of being infected and close contacts with known infected persons, or with PUI. Some of these were withdrawn, especially travel deferrals, within a few weeks due to the spread of the pandemic in the US and as additional issues were considered. Because of the concern for asymptomatic infection and rapid spread globally, SARS-COV-2 testing was recommended by the AATB physicians council panel, although FDA discouraged using laboratory tests to screen asymptomatic donors for COVID19 as the risk of transmission was unproven, and there were no approved covid-19 screening tests for tissue donors.
A study funded by AATB, investigated transmissibility from deceased tissue donors to determine whether the SARS-COV-2 virus RNA was present in their blood. Nine tissue processors were involved in the study, representing a significant portion of US tissue donors, and the results will be correlated/complementary to blood banking retrospective studies being led by Vitalant Research Institute. Another study supported by AATB will examine donors who tested positive by swab prior to donation. The study will sample several tissues (heart valves, myocardium, vein, artery, skin, adipose, tendon, bone osteochondral tissue) and the results will be correlated to non-human primate studies being done at the UC Davis centre.
The AATB has a Scientific and technical Affairs Committee with a subgroup on Emerging Infectious Disease (EID) assessment. This EID subcommittee has the aim to create a "procedure-like" approach for the AATB to evaluate emerging infectious diseases. The group is lacking a horizon scanning component, but hopes to implement this going forward in collaboration with multiple information sources.
To conclude, Dr Kuehnert noted that US regulations for blood, tissues and organs are different especially when related to the approval of laboratory screening, which creates issues when dealing with an emerging infectious disease that may be transmitted through transfusion and transplantation. Although the transmission risk of SARS-COV-2 through transfusion or transplantation is still unknown, there is a higher risk related to minimally processed tissues if there is virus tropism(e.g. live cells) and thus should be taken into account when focusing on surveillance for cases of transmission. There is a

need to coordinate risk assessment and a collaborative agenda among professionals, institutions and associations that could be useful when discussing how emerging infections can affect blood, organ and tissue safety accessibility.

- **Dragoslav Domanovic** – (*European Centre for Disease Prevention and Control, Sweden*)
  The lessons learned, outlined by ECDC, were related to the first wave of the COVID-19 pandemic in Europe. The SARS-COV-2 has spread across the world extremely fast, and in 9 weeks, the virus has affected all WHO regions. Compared to SARS-CoV and MERS-CoV, it has spread more rapidly. In the early weeks of the outbreak, almost two-thirds of the first cases in affected countries reported travel to China, Iran, and Italy. ECDC responded quickly by assessing the risk and recommending public health interventions, including the MPHO (referred to as Substances of human origin, SoHO, in the EU) safety measures (1st risk assessment issued on January 17th 2020). The identified risks were related to the viral safety of SoHO donors, recipients, the staff in hospital facilities and finally to the sufficiency and sustainability of SoHO supplies. The precautionary measures were focused on each group of SoHO and emphasised the activation and implementation of contingency plans.
  During the first wave in the EU Member States (MS), the reduction of blood donation numbers matched the reduction of transfusions, which prevented severe disruption to the blood supply. As of data from several MS, there was a median decrease of donations by 9% and a median decrease in the distribution of blood components by 12%.
  The European Medicines Agency (EMA) performed a survey among plasma manufacturing companies to assess the potential impact of COVID-19 on the supply of plasma or plasma-derived medicinal products (PDMP). Some disruption in the donation of source plasma has been reported whereas there were no reported shortages of PDMPs. The EU MS contingency plans ensured that there was no disruption in the supply of the EU markets. A key lesson was that the routine monitoring of plasma donation and availability of PMDPs is essential to ensure that no critical shortages will occur in the future.
  The presence of SARS-COV-2 in tears has triggered the implementation of preventive measures, which had an impact on cornea donation. Retrospective data provided by the Fondazione Banca degli Occhi del Veneto (FBOV) in Italy indicated that the lock down had resulted in the reduction of supplies, retrieval of corneas and demand for corneal transplantation. Finally, after the lock down, there was a slow recovery of supply. Additional information can be found at the link: https://journals.sagepub.com/doi/full/10.1177/1120672120948746 (last access: 20/02/2021).
  The numbers of organ donations and transplantations have also sharply decreased in EU MS during the pandemic. Dr Domanovic noted that the mortality of patients on waiting lists may constitute the significant collateral damage of the pandemic.
  Reproductive cell donation and related medically assisted reproduction (MAR) procedures were stopped in the EU at the beginning of the pandemic because of the uncertainties regarding the virus transmission. As the evidence became available and clear, this activity restarted.
  As regards to the increased vulnerability of immunosuppressed patients, data reported by the European Society of Blood and Marrow Transplantation on Covid-19 patients after transplantation (cohort of 398 post-hematopoietic cell transplant patients with Covid-19 from 20 countries) demonstrated that almost 21% died of Covid-19, 31% are alive and virus free (https://www.ebmt.org/covid-19-and-bmt (last access 20/02/2021)).
  Finally, since the beginning of the outbreak, no cases of Covid-19 transmission through SoHO have been reported. However, data shows that Covid-19 may affect the sufficiency and sustainability of SoHO supplies by reducing donor availability, affecting staff of SoHO facilities, changing the demand for products and limiting the provision or distribution of critical materials, equipment, and products.

It was highlighted that immunosuppressed transplant recipients are a high-risk population for Covid-19.
Dr Domanovic noted that the transfusion of convalescent plasma as a therapeutic option for Covid-19 could be considered in the absence of effective therapy or vaccination. Historical experiences of convalescent plasma use in related outbreaks and its immediate availability support such therapy. The growing pool of convalescent patients and the promising outcomes of initial case series and animal studies were good reasons to proceed studying this potential treatment. Further information on the EU programme of COVID-19 convalescent plasma (CCP) collection and transfusion at the link: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/guidance_plasma_covid19_en.pdf (last access 20/02/2021).
A new EU CCP database was established, to collect donation, safety, and clinical data. Results from various types of clinical trials and expanded emergency use of CCP showed the expected frequency of adverse transfusion reactions. More evidence, obtained in randomized controlled trials, is required to fully demonstrate the efficacy of CCP and to determine the indication, dosing and optimal CCP product characteristics.

- **Maria Angélica Salinas Nova** – (*National Institute of Health, Colombia*)
Maria Angélica Salinas Nova's presentation focused on the impact of the COVID-19 pandemic in Colombia. In Colombia the National Institute of Health (INS) coordinates the public surveillance system and its role has been strengthened due to the pandemic. The first diagnosed case of COVID-19 was reported on March 6th 2020. In the same month the INS issued the first donation & transplantation guideline and general guidelines for reporting cases in the national surveillance system, and granted continuity of transplant services in line with monitored capacity. The Second Edition of the guideline was issued in June 2020. Recommendations adopted for transplant dealt with the evaluating operational capacity, postponing or attending non-urgent medical appointments through telemedicine resources or home care, maintaining a virtual communication channel with patients, making appropriate recipient COVID-19 risk categorisation, strengthening pre-transplant studies and seeking informed consent from the recipient with all the information on donor-assignment risk, COVID-19 test results, or their absence, and inherent risk in the procedure under the circumstances of the pandemic.
Active surveillance in the country resulted in 84 COVID-19 transplanted patients being identified as well as 74 on the waiting list.
In summary, there was no suspension of activity in the country thanks to the confinement of the population. There was a higher impact on deceased donor versus living donor transplantation and limitations in the logistics of the process were identified. Insurance and the health system covered the cost of donor and recipient testing and their results were prioritised.
The need for increased trust in the population, through donation promotion, traceability and transparency, was highlighted. Self-care measures, in waiting list and transplant patients, needed to be strengthened. An action plan, to respond to similar treats, is needed, as is a focus on actions for vulnerable populations (immunosuppressive and chronic disease patients) and optimising the donation process (better coordinating donation teams and tissue banks).

- **Beatriz Dominguez-Gil** (*National Transplant Organisation, Spain*)
Spain was one of the most affected country in Europe by the COVID-19 pandemic. Even though the ICU capacity was increased by 300% to confront a healthcare crisis with no precedents, the Spanish Society of Intensive care was compelled to issue recommendations to guide professionals in difficult decisions regarding the allocation of ICU resources scarce to attend an exponentially .
The pandemic had a big impact on organ donation and transplantation rates, which dropped by 23% (deceased donors), 26% (live donors) and 19% (transplants) compared to 2019. Despite the low level

of activity from March to May 2020, from June 2020 the monthly rate of donation and transplantation has almost returned to 2019 levels. This reflects the capacity of the system to rebuild itself and adapt to the complex scenario posed by the pandemic.
Some critical points were highlighted for different aspects of donation and transplantation:

- A reduction in the potential of donations due to fewer admissions of patients with devastating brain injury patients in the most critical weeks;
- Failure to refer possible organ donors as in normal circumstances;
- Processes not implemented, due to hospitals and ICUs being overwhelmed;
- Potential donor losses due to COVID-19 active infections and logistical issues;
- Fewer transplants as a result of unfavourable benefits/risk assessments at a moment of sustained community transmission and limited COVID-19 free pathways;
- Transplants cancelled due to hospitals and ICUs being overwhelmed;
- Patients excluded for the WL due to active COVID-19;
- Patients unwilling to receive a transplant during the pandemic;
- Less availability of staff, as members of the coordination and transplant team had to isolate or were infected;
- The need to refocus staff on attending to COVID19 patients.

The transplant system was therefore rebuilt on three pillars. The first was to design new standards for the evaluation and selection of potential donors and recipients with regards to the infection caused by SARS-CoV-2 (*Dominguez-Gil B, et al. A J Transplant 2020*). The second was to build evidence of the safety of the new adopted standards and of the impact of COVID-19 upon recipients of solid organs and haematopoietic stem cells. An analysis of 778 patients who had acquired COVID-19 during the pandemic reveals no case of COVID-19 during derive infection, as well as the vulnerability of the transplant population to COVID-19 – with a higher cumulative incidence and higher case-fatality rate than the general population (*Coll E, et al Am J Transplant 2020*). Of note, the higher severity of COVID-19 in transplant patients is partly explained by their demographic profile and burden of comorbidity. The third pillar was to provide clear guidance to transplant centres on how to manage donation and transplantation programmes in a manner adapted to a heterogeneous and dynamic epidemiological scenario. It is emphasized that transplantation is an essential activity of the health-care system and must have the consideration of an urgent procedure that must not be deferred. Just in an epidemiological scenario 4, priority should be given to ideal donors and urgent or critically ill patients on the waiting list, as well as those difficult to transplant (paediatric and highly immunized).
During the discussion a question was asked of Dr Domínguez-Gil about which policy is followed when it is known that a potential donor has been exposed to someone diagnosed with COVID-19. When the meeting took place no specific guidelines were available. Considering the period of isolation and the symptoms at the time of donation, and the result of PCR testing, the clinician could be able to make the decision on whether to proceed or not. CDC and OPTN had no specific guidelines either. AST recommend that all donors be tested three days (72 hours) before the operation and the test repeated between 12 and 24 hours prior to the intervention. The same recommendation is applicable to tissue donors in the US. For living donors, it is suggested to cancel all donation if they had a contact with notified COVID-19 infected individuals. Non-urgent surgery can be postponed. Recommendations on this can be found in the ECDC's first RRA. (Risks posed by COVID-19 to the safety of substances of human origin (SoHO) supply assessed and response measures recommended https://www.ecdc.europa.eu/en/publications-data/risk-assessment-outbreak-acute-respiratory-syndrome-associated-novel-coronavirus) - last access 20/02/2021.

- **Dr Gamal Saadi, from the African Society of Organ Transplantation,** was asked to describe the situation in Egypt. The transplantation program there was restricted to Egyptians only, as the shutdown, prevented patients from other countries as Yemen, Libya and Sudan from traveling. In October 2020 in Egypt, donors were not tested for COVID-19, as there were no facilities to screen patients for the virus and depend on auxiliary laboratories and CT chest. Some hospitals were transformed to COVID services withholding the transplantation services yet most continued at a slower rate.

- **Christiane Costa, from ANVISA,** informed the audience about the measures adopted by the Brazilian authorities. Regarding Covid-19, Brazil has published several technical recommendations for products of human origin (blood, tissues, cell and organs donation) focusing on donor screening, considering the interval of 14 to 30 days after symptoms or risk exposure, besides hygiene and distancing measures and post donation information, as well. There is no laboratory screening for Covid-19 in the requirements for blood donation, but there are for donors of reproductive cells and also for cells, tissues and organs for transplantation (RT-PCR). Organs and tissues receptors are not tested in a mandatory way.
  Recommendations addressing convalescent plasma collection and use have also been published, both for experimental purposes (under clinical studies) and in emergency situations, including adverse events reporting. However, from the regulatory perspective, the NRA is not competent to oversee the results of clinical studies related to convalescent plasma (as a blood component).
  Concerning MPHO surveillance, there are no reports related to cells, tissues and organs, and one case for blood transfusion (based on post donation reporting) was under investigation. Then, the risk remains potential.
  In terms of availability there was an impact to blood supply that has been addressed by campaigns, donor scheduling and continued critical assessment of national blood stocks. Some recommendations implied a reduction in assisted reproduction procedures, which have been resumed in the perspective of a risk assessment and adequacy of establishments (focus on risk management). Same for transplants that had a reduction of about 30% in 2020. Tissue withdrawal from donors in cardiopulmonary arrest has been suspended but it has been resumed for ocular tissues. The impact on tissue removal was about 45%. Lately new recommendations focusing on the risk management for a gradual return of tissue bank activities were prepared.
  It was also necessary to adjust the processes for importing hematopoietic cells and gametes, considering donor screening, laboratory testing and restrictions on the movement of foreigners and flights.
  Due to Covid-10 pandemic, the Brazilian competent authority (Anvisa) anticipated the validity of the recent regulation applied to advanced therapy products, contemplating emergency use, not subject to registration, under medical responsibility.
  Difficulties in monitoring establishments with the restriction of on-site inspections and the absence of remote procedures for inspection, as well as for monitoring adverse events (underreporting, limitations on adapting existing tools, raising stakeholder awareness, etc) were reported. Another critical point is the continuous need for revisions and updates on the recommendations and testing algorithms, according to the state of the art of the pandemic, knowledge and demand. References to international recommendations were always followed, considering local specificities.
  The Brazilian Health Regulatory Agency (Anvisa) generated a contingency plan to assess risks in regulatory processes. These points should be considered in terms of lessons learned for the definition of future preventive measures.

  During the discussion a question was asked of Dr Gil about which policy is followed when it is known that a potential donor has been exposed to someone who has COVID-19. When the meeting took

place no specific guidelines were available. Considering the period of isolation and the symptoms at the time of donation, and the result of PCR testing, the clinician could be able to make the decision on whether to proceed or not. CDC and OPTN had no specific guidelines either. AST recommend that all donors be tested three days (72 hours) before the operation and the test repeated between 12 and 24 hours prior to the intervention. The same recommendation is applicable to tissue donors in the US. For living donors, it is suggested to cancel all donation if they had a contact with notified COVID-19 infected individuals. Non-urgent surgery can be postponed. Recommendations on this can be found in the ECDC's first RRA. (Risks posed by COVID-19 to the safety of substances of human origin (SoHO) supply assessed and response measures recommended https://www.ecdc.europa.eu/en/publications-data/risk-assessment-outbreak-acute-respiratory-syndrome-associated-novel-coronavirus - last access 20/02/2021.

In summary, some of the lessons learned were technical and others operational. It was extremely useful for the EU MS that ECDC officially highlighted, in its recommendations, that transfusion, donation and transplantation are essential activities. This not only encouraged people to go out and donate blood during the lockdown, but EU Blood Centres got PPE when it was in short supply and could only be given to those engaged in essential services. Finally, early on, there was a huge problem with the movement of bone marrow and peripheral stem cells around the EU because boarders between member states suddenly closed and transportation stopped due to the pandemic. **All these operational issues should be put together in a small paper on this subject and could be used to update a dedicated chapter in the booklet**. It should include a recommendation, as also highlighted in ECDC's recommendations, that a person with knowledge of MPHO should be involved in national crises committees that oversee high level measures, to highlight the importance of collecting and transporting MPHOs. Recurring themes highlighted by the presenters were related to communication issues and early and coherent messages to be shared. An effort should be made to allow quick access to international guidelines globally as early as possible.

October 2nd 2020

The first part of the second day was moderated by Michael Strong who outlined the history of the NOTIFY Project from its early stages until now, its tenth anniversary. The first part of the discussion focused on the overall update on the work done by the NOTIFY team and the 5 Editorial Groups (EGs) since the last general meeting, held in Brussels in March 2018.

Update on the NOTIFY Library (Evangelia Petrisli on behalf of the NOTIFY TEAM)

The first presentation, by Evangelia Petrisli, provided an update on the content of the NOTIFY Library. Since March 2018, a total number of 153 new records had been uploaded to the database and there are 149 new records in the editing process, out of which 50 are ready to upload. An additional 171 new proposed references have been collected for EG consideration (43 infections, 16 process, 85 clinical complications and 27 living donor reactions). Over the last two years, new instructive cases have been included and new MPHOs have been added to the Library, such as liver-intestine, cryopreserved adipose tissue and dendritic cells. New adverse occurrences have also been added, specifically new pathogen transmissions: talaromyces, Borna virus, Francisella, Japanese encephalitis and ureaplasma.

Currently the Notify Library users can consult juh1733 records linked to more than 2635 bibliographic references.

As far as the group members are concerned, the 'Who we are' section has been updated with the names of the Founder members, grouped as the Steering Committee of the project, with the aim of discussing strategies and the future of the project. In addition, new members have joined the Living Donor and the Clinical Complication Group.

Some major website changes have been implemented, most importantly the database content analysis section that includes 11 charts that summarise the number of Notify records and categories (by adverse occurrence or MPHO type) https://www.notifylibrary.org/content/database-content-analysis - last access 20/02/2021. These charts are continuously updated and can be used whenever members would like to cite the data in the Library.

Given the SARS-COV-2 pandemic, the safety recommendations for the MPHO section in the background document was updated with relevant documents and guidelines issued by international organisations and Competent Authorities: see https://www.notifylibrary.org/background-documents - last access 21/02/2021. Uploaded documents will be revised to remove the outdated ones.

A new version of the brochure and the general presentation are available in pdf[1,2] format and can be used by all Notify partners for dissemination purposes. As far as dissemination is concerned, in the past two years Notify was presented in 21 National and International Congresses and courses. Dissemination activities are reflected in an increase in the number of users monitored with Google analytics technologies. The two WHO regions whose activity has increased the most during 2018-2019 are AFRO and AMRO where activity almost doubled, most likely due to the workshop performed during the 1st African Society and the 5th Egyptian Society congresses. A publication providing an update on the project is in press in the Transplantation Journal[3,4],

along with another paper on incidents in the Medically Assisted Reproduction sector. EG members are encouraged to work on publications, given the important opportunity offered by Dr. Jeremy Chapman to host a Notify publication annually in the Transplantation Journal. A Notify session has been hosted in the second Congress of the African Society of Transplantation (ASOT, January 2021) and CNT is in

[1] https://www.notifylibrary.org/sites/default/files/NOTIFY%20LIBRARY_Brochure2018.pdf

[2] https://www.notifylibrary.org/sites/default/files/The%20NOTIFY%20project%20a%20general%20overview_Sept2020.pdf

[3] https://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=9000&issue=00000&article=95425&type=Abstract

[4] https://journals.lww.com/transplantjournal/Citation/9000/Donor_derived_disease__who_to_notify_.95424.aspx

contact with the OTA (Australia) for a space in their national meeting. Finally, in 2021, the project will attempt to organise an online meeting with all the editorial group members.

INFECTION (Ines Ushiro-Lumb, on behalf of the Infection Editorial group)

A total number of 604 records related to infections transmission are published in the Library. Specifically, 54% are related to organs, 20% to tissues, 18% to blood, 6% to cells and 1% to reproductive tissues & cells. In terms of adverse occurrence types, bacteria and viruses represent 35% each, parasites 16%, fungi 11% and prions 3%. During 2020, the work performed has been much reduced, due to the editors' involvement in the response to the COVID-19 pandemic.

The group has focused its effort on selecting case reports and case series offering learning opportunities. This can include new emerging infectious agents, involvement of MPHO not previously described, or first describe transmission event involving new or an established pathogen; Tick-born encephalitis and Borna disease virus were given as examples. Specific challenges can also be highlighted, for example, the difficulties in speciation of *Candida auris*.

Infectious agents well known to have been linked to donor-derived transmission events also merit mention whenever there is an opportunity to share experiences in a didactic form. Hepatitis B Virus (HBV) and occult HBV still attracts interest in the field of transfusion, with ongoing discussions regarding further opportunities to mitigate risk of transfusion-associated infections. Human herpes virus type 8 is another example, with post-transplant Kaposi's Sarcoma often assumed to be due to reactivation in a previously infected organ recipient, with no consideration of an infection of donor origin.

When there is controversy over specific themes, the editors' role is to provide background about the lack of consensus, the difficulties in obtaining robust data as well as the challenges faced in providing specific guidance. Rather than purely listing adverse events, the current aim of the NOTIFY Library is to concentrate on drawing the reader's attention to the learning opportunities from each event described.

LIVING DONOR (Anne Marie van Walraven, on behalf of the Living Donor EG group)

The work of the EG is conducted on a voluntary basis and new members are always welcome to support their work. New organ experts are requested, to enlarge the group. A total of 300 records are available on the Library, the majority related to HSC, followed by organs, bone marrow and blood. The majority is gathered under the category miscellaneous, then drug related reactions, infections, vasovagal reactions, and other complications.

The Living Donor group has three subgroups.

Subgroup 1 Blood: is led by Mary Townsend, with 3 reviewers (Mary, Mona Papari and Lizabeth Rosenbaum). The group currently has 2 records to edit, 4 with the first review completed, 3 ready to upload and 9 new references for consideration, which are not in the editing tool. Two recent papers, on the potential transmission of Sars-Cov-2, will be reviewed for possible publication in the Library.

Subgroup 2 HPC: is led by Anne Mary, who took the lead from Bronwen Shaw. The group also includes Thilo Mengling. This subgroup has 9 records ready to upload, 8 in editing, and no new references for consideration. What is remarkable for this subgroup is that living donor vigilance is being recognised as important, and the Transpose project (an EU funded project that looked at transfusion and transplantation protection and selection of donors) has prepared educational material (quizzes and webinars), which are available on the website https://www.transposeproject.eu/transpose-webinar/ - last access 20/02/2021.

Recently WMDA launched the Global S(P)EAR registry and, apart from all the donor unrelated registries that report their SEARs and SPEARs, this new global registry will be the start of the transplant centres, involved in related donor care, reporting adverse events in individual and family donors.

Subgroup 3 Organs: is working on a restart. Tim Pruett is leading this group, new volunteer David Paredes joined recently, but more volunteers are welcome. Currently there are 18 new references to evaluate, which are not yet in the editing tool. If additional experts can join the group, it will be appreciated.
The living donor taxonomy will be revised, to align it with the S(P)EAR classification, as stated by the WMDA and Transpose project team, and a devoted search on keywords will be developed to conform to the approach of the Malignancy group.

CLINICAL COMPLICATION (Barbee Whitaker, on behalf of the Clinical Complication Group)

This group evaluates complications, including adverse events and severe adverse reactions, associated with the clinical use of medical products of human origin: Organs; Tissues; Cells; Blood; Reproductive Tissues; MPHO Derived Medical Products; Other MPHOs (Milk, faecal microbiota, topical products of human origin).
The group is composed of Dr. Barbee Whitaker, as chair, and experts for blood, blood products, and others; Dr. Marian Macsai is co-chair and the expert in ocular tissue. Other experts are Dr. Manish Ghandi (USA) – cells, blood, Dr. Wendy Paul (USA) – blood, blood products, Dr Eduardo Muñiz-Diaz (Spain) - blood, cells, Dr. Jay Menitove (USA) – blood, blood products and Dr. Mauro Costa (Italy) – reproductive cells/tissues.
Once a publication or a new reference is identified and proposed, it is reviewed by the Editorial team for novelty and, if considered appropriate, it is assigned a NOTIFY record number and a first and second reviewer. Depending on the recommendation issued by the reviewers the reference is accepted, referred to another editorial group, added to Background documents or rejected. The group currently has 104 new publications/references identified for initial review, 26 Blood Transfusion/Infusion references unassigned, 1 IVIG and 58 Transplantation references respectively, 5 Tissue (composite, bone, cardiac allografts), 1 Cornea, 20 Cell (BMT, SCT, etc.), 30 Solid organs (3 Heart, 8 Kidney, 9 Liver, 2 Lung, 2 Small Bowel, 6 general), 2 Reproductive cells, 20 Blood Transfusion/Infusion in the editing tool/process, 5 First review complete and 4 Unassigned (IVIG).
New experts are needed for the following topics: IVIG, solid organ, plasma derived therapies, tissues and cells.

PROCESS (Scott Brubaker, on behalf of the Process Editorial group)

The process group evaluates process failures that affect desired MPHO characteristics, clinical utility or availability for use. The group is co-chaired by Dr. Mauro Costa (Italy) – reproductive cells/tissues; and Scott Brubaker (USA) – organs, tissues, cells and "other". Other members of the group are: Paula Nolan (UK) – reproductive cells/tissues; Jennifer DeMatteo, MCM, CIC (USA) – ocular tissues; Alessandra Alteri, PhD (Italy) – reproductive cells/tissues; Paul Ashford (UK/USA) – blood/blood products, plasma.
The group has 5 new publications that need an initial review, 2 related to platelets and 3 'Type not specified' (2 donor blood samples and one blood typing). Fourteen publications have been reviewed and are pending next steps, some of those seem suitable for the Infection group.
Nine publications will be entered as new records. Three for blood (platelets); 2 for Organs (kidneys); 1 HPC and cord blood); 1 for faecal microbiota and 2 for amniotic membranes and placenta.
This group is seeking additional expertise in organs and cells as well. It is worth noting that most process related errors are not always published in scientific literature and this is where the annual SARE report of the vigilance agency becomes important. For the Library, it is important to capture such errors, because they can be critical (i.e. discarding kidneys during transportation, wrong blood in tube for donor testing).

MALIGNANCY (Michael Nalesnik on behalf of the Malignancy Editorial group)

The current members of the group are Mar Carmona, Carl-Ludwig Fischer-Fröhlich, Kathy Loper, Kerstin Moench and Michael Nalesnik and they all work together to contribute to the results. The Malignancy group has collected a total number of 338 records. The majority of these (258) are related to recipient harm in one form or other, rare reports are listed under donor harm, and a slightly larger number under risk of harm. There are presently 44 records in the editing stage, with 30 of these ready for uploading.

In the last few years, the editorial group has focused its activity on how to enhance its records. They have focused first on the malignancy classification, as well as on the estimated risk field. The group have identified its own approach to the keywords and put a lot of effort on the experts comment section.

The current listing of malignancy types is the result of a huge effort and it has now grown to include the various organ or organ system categories, with individual tumours listed beneath. There are 48 different types of tumours listed on the website. However, the total list includes 162 choices, but they will not show up on the website until there is at least one record, to prevent searches coming up with no results. Carcinoma of unknown origin and tumours of multiple types are also listed. Those usually show up in review articles, and the EG try to list the individual tumours in the keywords.

As far as the estimated risk for individual tumour types is concerned, the overall numbers of tumour transmissions are vanishingly small, when you consider the total number of transplants, and it was realised that what people really want to know is how often a given tumour type can be transmitted when it is present in the donor. Among the several risk stratification systems available, the most thorough is the one included in the Council of Europe Guide to the Quality and Safety of Organs for Transplantation. Recommendations from the 2018 (7th) edition have been used to complete this field. A new edition is in preparation and this will require appropriate updates if there are any significant changes for the content of the Library. Several members of the editorial group contributed to this chapter of the Guide so any updates will be immediately identified.

The EG have reviewed the entire list of keywords present in the database, including records submitted by the other groups, to see if there was relevance for malignancy. If there was, they added the keyword "malignancy" without altering anything else, so that a keyword search for malignancy would call up all malignancy records in the database, and only those records.

The group adopted a uniform approach to adding keywords and divided them into 4 categories, namely:

1) Report type (allows the user to search for review articles, single centre series, case reports),
2) Malignancy taxonomy;
3) Donor type;
4) Recipient/Transplant type is redundant with the dropdown boxes at present.

A fifth category Demonstration of Imputability is planned and will allow the user to search for proven cases or expand to other types for study.

The subject of report types arose when the group was trying to decide whether to include sources such as registry series, or subject reviews, since the original purpose was to document original reports of cancer transmission. It was decided that these reports had useful information but, to avoid any confusion in the record title, it should be specified that the document was a review or report. Record types by malignancy are categorised as follows: 54% as case reports, 15% as single centre series, 19% as reviews, 1% as editorials and 11% as registry series. Therefore, having the category as a keyword also allows the user to search for a specific document type.

One problem that has evolved is the result of different people using a variety of keywords to describe similar things over a period of years. The group has prepared a list of preferred keywords and plans on adding these as appropriate to strengthen the search capabilities.

Finally, another gap is how patients are treated when they have cancers. This was not the original main intent of the Library, but within the group it was agreed that, rather than list every possible treatment,

they will add the keyword "therapy" to the records as appropriate, which will allow the user to find records that discuss the treatments given, and the outcomes.
Future activities include adding current records, and preparing some dissemination material, possibly a publication describing the capabilities of the Library and what can be done in specific fields. A YouTube video, walking the user through different types of searches, would be helpful as well. As a proposal for IT development, part will be to filter the records in chronological order, so that the current experience can be separated from the historical papers in this area.

Summarising the first part of the meeting, during the discussion participants were reminded of the opportunity to join editorial groups or suggest new experts, depending on the field of expertise and to be considered by Chair and Co-chair and the Team. All participants are encouraged to share their annual vigilance reports (public document) with the NOTIFY Library, because they can be of high value for the editorial groups. All reports would be anonymised and referred to as vigilance reports coming from a specific WHO region. The procedure was developed during the VISTART Joint Action[5], to support the European Competent Authorities in selecting relevant cases in an anonymised way. The same procedure is applicable to any vigilance authority that would like to share instructive information. It was also mentioned that, at least in Europe, linking the vigilance report to the NOTIFY library can be discussed with the Commission as to whether this should be formalised.
Papers can also be submitted for review, in addition to the alert that the team is already receiving from OVID, Google scholars, sending them directly to notifylibrary@iss.it.
David Paredes volunteered to take part to the Living Donor group.

The second part of meeting discussion was moderated by Efstratios (Stratos) Chatzixiros (WHO Consultant on MPHO) and had, as a key topic, the possibility of building a global horizon scanning and MPHO preparedness network. The suggestion was that the network could take advantage of the NOTIFY library as a channel to share timely information to relevant/key stakeholders in the event of future outbreaks, to secure quality, safety, availability and access to MPHO products and services. The session was split in three parts:

1) problem definition by the different scientific societies, the mechanisms available and how they could be harmonised;
2) a round table discussion about what the NOTIFY project can do and how the WHO should be responding to that need;
3) Defining a possible action plan.

PART 1

As far as the problem definition is concerned, a panel of experts, representing international MPHO associations, was invited in advance, to respond to 4 questions:

1. How does a professional society inform itself on emerging diseases and outbreaks?
2. In this context, is there any structured interaction with established national or international institutions or public health authorities?
3. Is there a structured mechanism for notifications – alerts to your members regarding emerging diseases?
4. Do you have procedures in place for the development of preparedness plans and guidance in the case of disease outbreaks?

Anna Veiga – European Society for Human Reproduction and Embryology (ESHRE)

[5] https://www.notifylibrary.org/sites/default/files/VISTART_WP5A_A%20User%20Guide%20for%20CA.pdf (last access 20/02/2021)

ESHRE created a working group[6] to prepare statements and initial guidance documents, gather information about ART/MAR and COVID-19; answer queries from professionals and patients; monitor MAR activities in Europe during the pandemic[7]; prepared a survey to get case reports from professionals who had COVID-19 pregnant patients, at the time of initiating a pregnancy, and eventually to draft guidance on restarting activities after the first wave of the pandemic[8].

The group is working with published data, information gathered from ESHRE National Representatives, data collections on pregnancies and with the support of experts from other professional societies.

Most of the information about the centres' activities was provided by the national representatives (two per country). ESHRE liaised with ECDC, WHO and other organisations, to gather more information. Several guidance documents were produced and papers published in journals. There were also joint efforts with the American Society for Reproductive Medicine and the International Federation of the Fertility Societies[8]. These efforts involved webinars and sessions in their annual virtual meetings and the launching of a research grant. ESHRE is monitoring the data on COVID 19 pregnant patients and outcomes, to see the impact on mother and child. All the information was shared through existing communication channels, via email, with a dedicated website and through social media channels.
As far as interaction with national competent authorities is concerned, ESHRE, as a scientific society, does not have any official responsibility, but despite not having contacted authorities or ministries of health in EU countries directly, most of them have adopted ESHRE guidance documents as a gold standard to identify what needs to be addressed in MAR activity. ESHRE shared all relevant information with the European Commission and ECDC, including ESHRE recommendations on ECDC documents or SoHO safety.

Graeme Pollock (Australia), representing Global Alliance of Eye Bank Associations (GAEBA)
GAEBA is a global organisation of 6 eye bank associations that cover America, Europe, India, Oceania, and parts of Asia. One of the goals of the association is the development of promotion coding, traceability and vigilance systems for ocular tissue. The implementation of all the tools for vigilance and surveillance have been diverse around the globe but the traceability from donor to recipient is well established and coding systems are also in place.
As far as the true surveillance system is concerned, it is worth underlining that in the US, EBAA has an excellent system in place and data is reliable. This is pivotal, as the US is responsible for 1/3 of cornea transplantation in the world. Australia and New Zealand have a system which is similar to that in the US. In this regard, the robustness of a system comes from the kind of resources allocated to support its activity, and the extent of eye banks' involvement in the system, whether data reporting is mandatory or not. In the US system, reporting is mandatory, through the accreditation system that the EEBA has in place. Because of the transnational scope of GAEBA and cornea transplants, follow up is difficult and this reflects on reporting of adverse events.
There is no global agreement on Horizon Scanning. It is more a sharing of information among GAEBA members. In Australia, where there is no CDC in place, they use the information collected by the national blood service, which performs horizon scanning. The information therefore goes to the medical advisory committee of the professional society and results in the production of dissemination guidelines for the eye banks. The Global alliance benefits from this kind of documentation, which relies on the expertise of the committee.

[6] https://www.eshre.eu/COVID19WG (last access 20/02/2021)
[7] ESHRE COVID_19 working group et al. A picture of medically assisted reproduction activities during the COVID-19 pandemic in Europe https://academic.oup.com/hropen/article/2020/3/hoaa035/5893474 (last access 20/02/2021)
[8] https://www.eshre.eu/Europe/Position-statements/COVID19 (last access 20/02/2021)

Marisa Herson- WUTBA World Union of Tissue Banking Associations

WUTBA is the World Union of Tissue Associations, formed in 2005. It brings together the 5 largest associations of tissue banks and, most recently, SATIBA (the South African Association of Tissue Banks), which joined as an observer member. The Secretariat has the ongoing role of "surveillance" and they meet every three months with the Executive council. This proved to be a very productive way of updating all the associations. When needed, there are ad hoc communications with members. The WUTBA web page www.wutba.org is updated after the Executive Council meeting takes place or whenever there is important information to be shared.

WUTBA does not have direct interaction with established national or international institutions or public health authorities but regional Associations have their own direct interactions. There is a direct approach, to gain insight and ensure sharing, which was especially useful during the pandemics. WUTBA relies on its association to disseminate relevant information beyond the confines of the Executive Council Representatives.

Within 24 hours, the association can reach 70% of its Tissue Banking activity through this channel, when there is a need to proactively alert members. WUTBA does not have its own preparedness plan or guidance related to disease outbreaks. The Union has challenges but one of its biggest concerns is that a large amount of tissue is used in countries where there is no tissue banking activity, no surveillance and no awareness by the authorities that the tissues are being used. When this happens, surveillance and reporting of adverse occurrences are impossible.

Francis Delmonico, on behalf of Elmi Muller - the Transplantation Society (TTS)

The professional societies TTS and the American Society for Transplantation, AST bring together professionals who, in their role for the society, acquire information regarding adverse effects and complications and safety & quality of organ donation & transplantation. These societies also interact with regulatory authorities, the Organ Procurement and Transplantation Network (OPTN) and the Donor Transplantation Advisory Committee (DTAC), are examples of this type of liaison.

The AST developed a chat line to allow information to be shared immediately regarding testing and experience with the donor population.

The WHO has a clear responsibility for quality and safety and NOTIFY can secure, from professional societies, a complementary representation, to help the WHO to achieve these objectives, by improving awareness and, to a greater extent, to reach all MPHO and societies. These professional societies provide information to their members.

Dietger Niederwieser – Worldwide Network for Blood & Marrow Transplantation (WBMT)

The WBMT is a federation of societies (22 societies working in special aspects of stem cell transplantation). WBMT oversees more than 1600 transplant centres in 82 countries that communicate with the society directly, is in working relation with the WHO and with their national authorities. 1.5 million activities have been compiled and published.

Reporting is a key element related to transparency on activity and traceability. WBMT is working on a transparency registry for future use, with the help of other international organisations. The association has contacts with regulatory authorities. However, WHO could help to improve the relationship, especially in countries where no national authority established.

During the COVID-19 pandemic, guidelines of how to transplant stem cells in a safe manner were published9 on the website.

The WBMT is collecting the activities worldwide on first stem cell transplants. In 2006 more than 82000 were performed and in 2008 90.000 were reached. Nowadays also outcome analysis were performed

[9] https://share.wmda.info/pages/viewpage.action?pageId=344866320

worldwide. Side effects can be handled were quickly around the world (e.g. nuclear accident in Fukushima; shortage of medicines).

Paul Ashford - ICCBBA

ICCBBA has a network of approximately 250 subject matter expert volunteers representing all areas of MPHO and spread around the globe that form the ICBBAA Technical Advisory Groups (TAG). Many of these experts act as professional society representatives so are well informed on developing priorities. Some of them also represent regulators in different countries. Those TAGs provide an effective communication channel to raise awareness of emerging disease and outbreaks that are identified as part of their routine agendas during their meetings. ICCBBA staff are themselves members of professional societies and monitor scientific publications.

ICCBBA first became aware of the developing outbreak of COVID-19 through news media and information received through WHO and NOTIFY. Discussion within the NOTFY forum was very helpful to provide additional information on what was developing. The first request for product description codes for COVID-19 Convalescent Plasma was received on February 25th, 2020. They were able to fast-track the allocation process and the first code was published, in an interim release of the product database, on March 5th, 2020. ICCBBA raised awareness of this through the TAG networks and via the official website and social media posts. Since then, they have been releasing new codes on request, and are currently adding codes to accommodate the recent FDA EUA Decision Memorandum to require indication of High and Low Titer information.

Mauricio Beltran – Pan American Health Organization (PAHO)

The PAHO region (which includes 52 countries and territories in North, Central, and South America) commented that the regional blood and transplant strategy is more developed for Hemovigilance and Biovigilance, especially in the countries of South America. Last year the ministries of health of the Americas approved a regional strategy and action plan to increase equitable access to organ, tissues, and cell transplant. The plan includes 4 strategies: 1) Strengthen health authority governance and stewardship in the cell, tissue, and organ donation and transplants, especially its oversight capacity; 2) Increase the availability of organs, tissues, and cells through voluntary non-remunerated donation; 3) Increase equitable access to organ, tissue, and cell transplants in health systems; 4) Improve information management, monitoring, surveillance, risk evaluation, and risk management activities related to organ, tissue, and cell donation and transplantation. In this context, PAHO has been working with Latin American and Caribbean countries, ONT - Spain, and INCUCAI in Argentina. Together, they have produced some technical guidelines. Regarding blood, there is strong cooperation with the Iberoamerican cooperative group in transfusion medicine GCIAMT to support the development of transfusion medicine and blood banking in the Region. In the countries of the PAHO region, blood programs are under development and hemovigilance is one of the objectives. Brazil and Colombia are already implementing vigilance systems for organs and blood, but other countries still need WHO assistance to develop similarly, especially in the areas of donation and transplantation.

<u>PART 2</u>

During the open discussion, several questions were raised: what can the NOTIFY project do? how should the WHO be responding to the need to create a link for future responses? how should communication channels be structured? and should the experts have a place where they could meet before issuing any advice on the safety of MPHO?

All the contributions highlighted that all the organisations and professional & scientific associations address the need to respond to such outbreaks as best they can. Without being too ambitious, one idea could be to have a small group of experts, that speak among themselves on a regular basis,

discussing what is emerging around the world, what they know and how it is impacting on each sector. One of the big strengths of NOTIFY is that it has always put together a mix of experts coming from different fields, regulators, professionals, infectious disease experts and public health agencies. The website could play a role in the dissemination of rapid alerts.
The language problem is still an issue and technology could help in merging all the information available. PAHO could be involved for Latin American Countries and representatives from Africa and the Asia Pacific region should be involved. WHO has to be the one to bring together the experts and notify the submitter of the information. Nevertheless, to support such activities, WHO does not have sufficient resources or capacity and will need professionals and scientific societies from different regions to be involved. The key issue is that NOTIFY already has a mechanism, as a network and a large pool of experts, thus it would be possible to take advantage of what already exists, as opposed to creating a new mechanism. This would require some effort from professionals, since it is voluntary work, and WHO will need to identify a way to support it, making it official and investing resources, considering the added value of working remotely, to facilitate discussion at minimal cost.
Channels that are already in place in the world can be considered in developing our strategy, globally or at a regional level. The developed global strategies to guide safety, such as the ones for drugs and vaccines, are examples.
A methodology on how to use the NOTIFY forum to host regular videoconference meetings might be an initial option.
The role of NOTIFY should be considered in two parts: 1) detection 2) Disseminating news and pushing communication to all organisations involved. During the pandemic it was very useful to use the chat facility, as it brought professionals together. Finally, NOTIFY could provide a platform where people can get together for this purpose with the significant advantage of being able to cover all MPHO. Different recommendations have been provided by different scientific societies but these are fragmented and contain considerable overlap. There could be an opportunity for NOTIFY to assemble a combined statement or even harmonise recommendations.
WHO should encourage the WHO regions and advise professional associations to join the NOTIFY initiative and promote the Library. Establishing a global advisory committee would be a bit difficult, as it would be require the official endorsement of the DG and be proposed by all the Members states. In a first stage, the NOTIFY platform can be used to trial a possible working group and afterwards, if shown to be useful and well recognised, then every member state could be asked to propose that a stronger committee be organised under the WHO umbrella.
To move forward, the first step would be to prepare a Terms of Reference for this working group, describing the necessity to develop a network at a global or regional level. The ToR would identify the internal communication path and a possible link to EIOS. NOTIFY's capacity could be used as a technical advisory group on all MPHO.
As far as ECDC is concerned, the group could be a point of contact with the EPIS system and large public health institutions, for the timely receipt of information. The group could be an instrument of WHO, and WHO could also contact this group and NOTIFY and then NOTIFY would analyse and disseminate the information.
There was agreement that the real value of NOTIFY lies in its ability to link or correlate the emerging disease (e.g. the spread of a new virus) to the MPHO and its use in transfusion and transplantation. In this sense, NOTIFY, under the umbrella of WHO, could be a reliable information source for authorities during outbreaks.
WHO can also help to develop regional forums than link to national regulatory authorities, such as the one that has been created for the African Blood regulators forum. In the field of blood, NOTIFY tools (the booklet and information from the background document) will be given to participants attending the ISBT-WHO-Hemovigilance workshop involving Zambia and Burundi

ACTION PLAN

Given the consensus on the need to establish such a group in NOTIFY, platform volunteers were requested, to establish a small WG to address the issue in a sample paper. Building on something that works well would give the WHO the chance to endorse the new group or make it part of WHO's established group of experts.

Take-home messages

The COVID-19 pandemic is an unprecedented global crisis that affects every aspect of our lives. It also has tested the sufficiency and sustainability of the MPHO supply, even though it poses only a theoretical safety risk. The extensive spread of the diseases, combined with its high morbidity and mortality, public health interventions and precautionary measures all acted in chorus on the MPHO supply by decreasing donor availability, unpredictably affecting the demand of MPHO and limiting the provision or distribution of critical materials, equipment and products.

The pandemic and previous outbreaks of emerging infectious diseases, have demonstrated that the early detection of an outbreak is a prerequisite for a timely response, based on adequate risk assessment and recommendations on appropriate public health interventions, including measures to maintain the safety of MPHO. Horizon scanning or epidemic intelligence is a core activity of international/national/regional public health bodies, like CDCs and WHO or ECDC. Once identified, MPHO threats should be communicated to relevant experts in the response bodies, who assess the risk of infectious diseases transmission through MPHO and recommend preventive interventions.

In this respect, the NOTIFY Library took the initiative to improve preparedness for future outbreaks. Considering the global character of EIDs, better international collaboration, with stronger links among governments and/or regulatory authorities, public health services and MPHO establishments or producers, has been proposed. Action is also needed to facilitate networking among researchers and clinicians, MPHO experts and services. Establishing the framework (network) at international levels may contribute to the better management of MPHO risks that are of global concern. The NOTIFY Library can host an international network that can analyse the detected threat, assess the risk and recommend appropriate measures. It may also provide a structured library of documents related to maintaining the safety and sustainability of MPHO supply.

Keeping MPHO safe - monitoring adverse outcomes and scanning for new threats.
A Joint ECDC and WHO Notify project meeting
October 1st and 2nd 2020 – ZOOM platform

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16	Paul Ashford	UK
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19	Scott Brubaker	USA
20	Eduard Muniz	Spain
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22	Wendy Paul	USA
23	Barbee Whitaker	USA
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25	Lizabeth Rosenbaum	USA
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27	Lydia Foeken	The Netherland
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29	Kathy Loper	USA
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